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CASE SERIES

Using Hydrating and Re-Epithelizing Gels as an Adjuvant Treatment of Fractional CO_2 Laser in the Management of Genitourinary Syndrome of Menopause: A Clinical Case Series

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Abstract

Genitourinary syndrome of menopause (GSM) is one of the most prevalent conditions linked with the menopause and greatly impacts the quality of life. In this prospective cases series studies, 22 patients of 60 ± 6.34-year-old were treated with niosomal hyaluronic acid and *Centella asiatica*-based vaginal gel as an adjuvant treatment to the CO_2 laser therapy for the GSM for 5 months. The aim was to assess the microbiota improvement along with other parameters related with GSM. After treatment, the amount of *Lactobacillus spp*. population was significantly increased from 4.23 ± 2.23 to 5.36 ± 2.50 log CFU/g. Specifically, *L. gaserii* from 1.66 ± 1.60 to 2.49 ± 1.48 log CFU/g and *L. inners* from 1.47 ± 1.5 to 2.64 ± 2.7 log CFU/g, respectively. Importantly, *Enterobaceriaceae spp*., showed a significant decrease after treatment. Other variables such as a significant reduction of vaginal pH from 6.68 ± 0.46 to 5.5 ± 0.56 log CFU/g, a significant increase of Bachman index from 10.27 ± 2.29 to 16 ± 2.18 log CFU/g. Lastly and improvement of Sandvik index from 2.52 ± 2.61 to 1.09 ± 0.81 log CFU/g were observed. FSFI significantly improved after treatment from 2.14 ± 1.45 to 3.08 ± 1.41. 95 log CFU/g. 5% of patients declared being satisfied or very satisfied with the treatment. Hence, these results point that this therapeutic approach might be useful for the management of GSM; new controlled studies must be done in other to fully determine its effectiveness.

Keywords

Niosome, Hyaluronic acid, *Centella asiatica*-based vaginal gel, Prebiotic, Fractional CO_2 laser, Genitourinary syndrome of menopause, Adjuvant treatment

Introduction

Together with vasomotor symptoms, the genitourinary syndrome of menopause (GSM) is the most frequently reported condition during this period of women's life [1,2]. It is estimated that around 50% of women will develop GSM at some point in their post-menopause; although having different intensities, it is thought that its incidence is underestimated [3]. The most prominent symptoms of GSM are irritation/burning/itching of vulva or vagina, vaginal dryness, inadequate lubrication during sexual relations, dyspareunia, postcoital bleeding, changes in the frequency and urgency to urinate and incontinence [4,5]. Importantly, some studies have shown that GSM can negatively impact quality of life (QoL) mostly conditioning daily activities and sexual health [6,7]. Hence, an active action by health care professionals is needed to identify this issue in population at risk and actively search for solutions adapted to each patient needs.

Regarding the available treatments, the most frequent therapeutic approaches are local oestrogen treatment and the use of hydrating products such as hyaluronic acid gels [8,9]. However, some recent reports show that the fractional CO_2 laser can be a useful therapeutic tool for the treatment of GSM associated with menopause [10-14]. On one hand, some of these

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studies have shown that laser therapy improves vaginal health as well as Quality of life (QoL) of menopausal women. On the other hand, the tissue regeneration response induced by CO_2 laser treatment seems to generate an environment that facilitates *Lactobacillus spp.* grow due to the new tissue and collagen formation [12-16].

Many of these symptoms are effectively treated with local application of menopause hormone therapy (MHT). However, not all women wish or are eligible for MHT or they are not eligible due to either safety concerns (i.e cardiovascular problems, thromboembolism or endometrial cancer) or more advanced age [17-19]. In this regard, laser therapy might be particularly useful medical alternative for those women that have a reduced QoL dure to GSM but they don´t wish or are not eligible for some MHT.

Some other studies have shown that another interesting property of laser treatments is that they create microchannels in the epidermis allowing a very efficient permeation of locally applied products, generating a synergistic effect [20,21]. Nonetheless, there is few clinical evidence describing how CO_2 laser can produce a synergistic effect with locally applied products increasing clinical benefit for those patients [21,22].

Hence, we decided to prospectively observe the effect over the vaginal microbiota, together with some signs and symptoms frequently associated with the GSM of the combination of a CO_2 laser with an adjuvant treatment with a niosomal hyaluronic acid, *Centella asiatica*-based vaginal gel which know hydrating, re-epithelizing properties. We aim that the data presented from this series of cases can be used as a starting point for new controlled studies that fully determine the clinical advantage of this medical approach.

Methods

This was a prospective case series study, including menopausal women who came for consultation due to signs/symptoms associated with GSM. Study scheme is shown in figure 1**.** All women had 3 visits. At the initial consultation, patients were treated with CO_2 Laser (Multisys®) with a setup of 90-110 mJ, 0.2 ms, 13 density using an hexagonal head and random scanning mode plus an adjuvant treatment with a niosomal hyaluronic acid, *Centella asiatica*-based vaginal gel (Palomacare® Vaginal Gel). The gel was used immediately after each laser session and then, daily for a total of 6 days. After that, it was used every other day until the next laser session, approximately 6 weeks later. During the second consultation, patients were treated again with CO_2 Laser and the product was immediately applied as in the previous consultation. Then, niosomal hyaluronic acid, *Centella asiatica*-based vaginal gel was used daily for 5 more days (6 days in total). Both laser sessions were separated by 5 weeks approximately. Finally, measurements were taken 15 days after the last laser session during the third and last consultation.

The main data collected was the composition of the vaginal microbiota, which was assessed by PCR (Teletest Laboratories). Other collected data were, Bachmann index for vaginal health, which evaluates 5 parameters: overall elasticity, type and consistency of fluid secretions, pH, epithelial mucosa, and vaginal moisture. It assigned values from 1 to 5. Sum of the five scores defines total VHI score, the pH, Female Sexual Function Index (FSFI), is self-report questionnaire designed to measure sexual functioning in women. It assesses six domains of sexual function: sexual desire, sexual arousal, lubrication, orgasm, satisfaction, and pain. The Sandvik severity index, which measures the severity of urinary incontinence symptoms through 2-item questionnaire. Lastly, the patient satisfaction was also measured with a 0 to 10 Likert scale, (completely unsatisfied from 0 to 1; unsatisfied from 2 to 3; somehow satisfied from 4 to 5; satisfied from 5 to 7, and very satisfied from 8 to 10) all the questionnaires were self-assessed by each patient.

These series of clinical cases were collected at the Sagrada Familia Clinic, Barcelona, Spain. As patient-

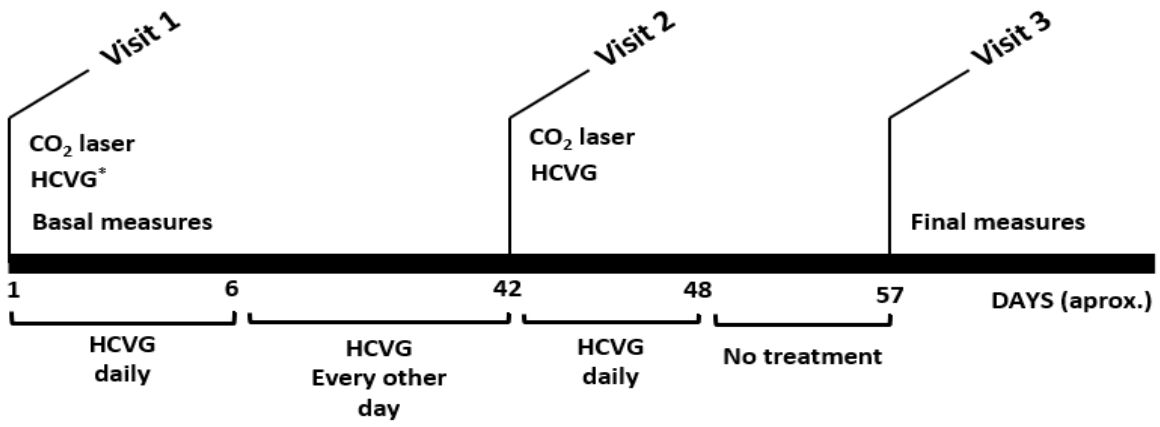

Figure 1: Diagram shows the different visits that participants attended to treat the genitourinary syndrome of menopause. *HCVG: Hyaluronic acid, *Centella asiatica*-based Vaginal Gel

specific information was deidentified to ensure anonymity, patient consent was not necessary. The inclusion criteria were menopausal women who had no period for at least the last 12 months, all of them attending to the consultation due to symptoms associated with the Genitourinary Syndrome of the Menopause (GSM), including reduced vaginal health and reduced sexual function, and who could read and understand the informed consent and having a feasible follow-up. As exclusion criteria, women who had induced menopause, due to hysterectomy or different treatments, such as Radiotherapy or brachytherapy, any patient with relevant immunological alterations, any type of immunosuppression or any other relevant condition that was considered relevant. Also, patients that had not feasible follow-up will be included.

Results

22 menopausal women between 50 to 71-year-old (average age of 60 ± 6.34 years) were evaluated. We found a swift of the bacterial microbiota composition, as the overall *Lactobacillus spp*. population significantly increased after the treatment from 4.23 ± 2.23 to 5.36 ± 2.50 log CFU/g, figure 2A**.** Within the lactobacilli populations that were increased, *L. gaserii* from 1.66 ± 1.60 to 2.49 ± 1.48 log CFU/g and *L. inners* from 1.47 ± 1.5 to 2.64 ± 2.7 log CFU/g, figure 2B and C, respectively. Other lactobacilli showed not significant increases: *L. crispatus* from 3.21 ± 2.45 to 3.52 ± 3.01 log CFU/g and *L. jensenii* from 1.93 ± 1.71 to 2.18 ± 1.80 log CFU/g and, figure 2D and E respectively (Supplementary Figure 1A and 1B). On the other hand, other lactic acid producing bacteria were also studied but none of them

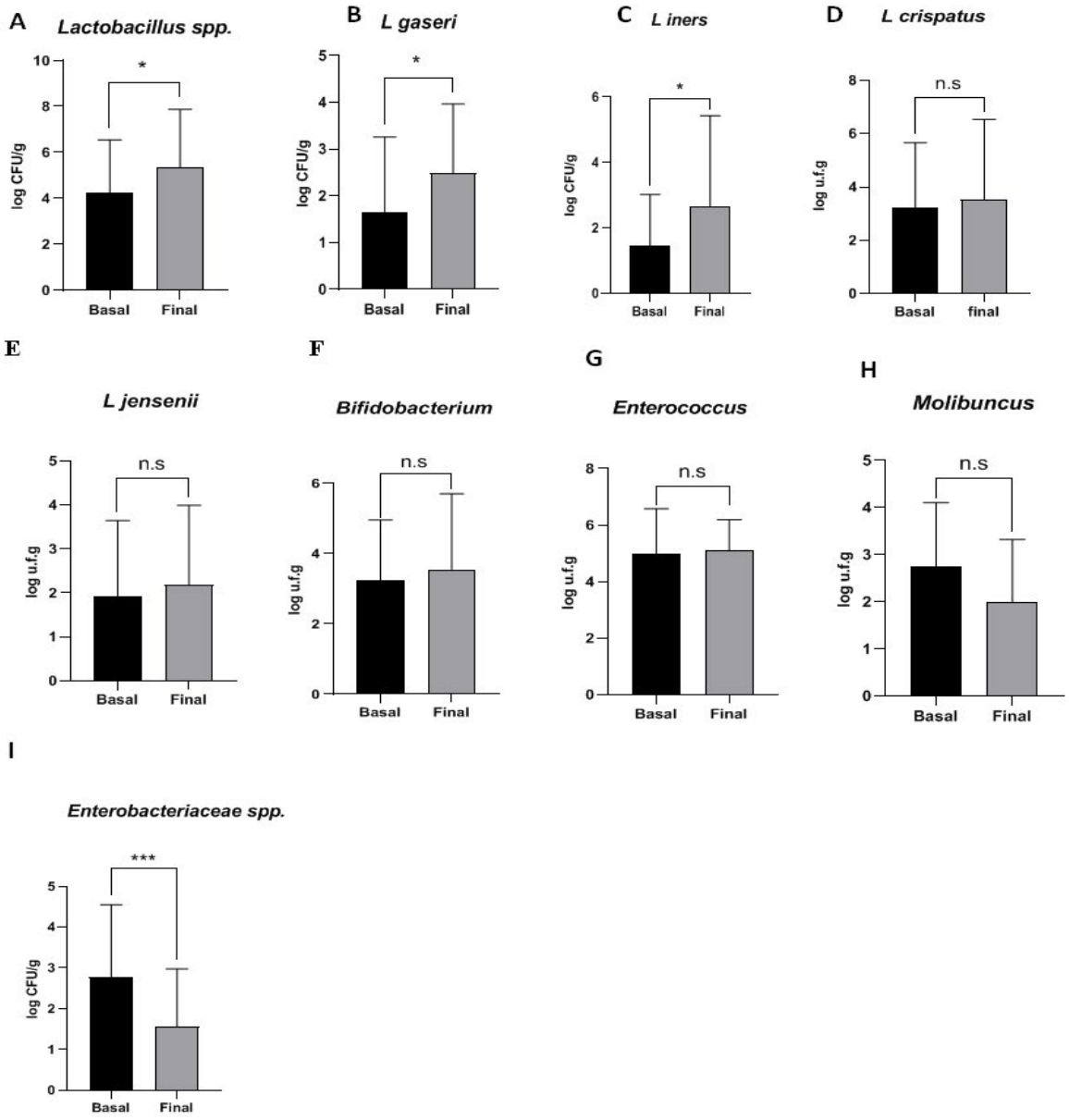

Figure 2: Changes in the amount of different lactic acid producing bacterial species, that are frequently part of vaginal microbiota composition: (A) *Lactobacillus spp.*; (B) *Lactobacillus gaseri*; (C) *Lactobacillus iners*; (D) *Lactobacillus crispatus*; (E) *Lactobacillus jensenii*; (F) *Bifidobacterium spp.*; (G)*, Enterococcus spp.*; (H) *Molibuncus spp.*; (I) *and Enterobacteriaceae spp.*; log CFU/g: Colony Forming Unit per gram; n = 22; * $p < 0.05$, *** $p < 0.001$ paired t-student with Welch's correction post hoc test.

were significantly modified, figure 2E, 2F, 2G and 2H (Supplementary Figure 2A, 2B and 2C). Non-lactic acid producer bacteria were also studied, from this group *Enterobacteriaceae spp.* were a significantly decreased from 2.76 ± 1.77 to 1.55 ± 1.42 log CFU/g, figure 2I. All other studied non-lactic acid producing bacteria (*Bacteroides spp., Prevotella spp. and Staphylococcus spp.*) were not significantly modified (Figure 3A, 3B and 3C) (Supplementary Figure 3A, 3B and 3C). Finally, Chlamydia, Candida, Mycoplasma and Ureaplasma also did not showed any significant presence in all 22 patients (**data not shown**). A summary of all the analysed bacterial populations is showed in table 1.

Regarding other outputs, we observed a significant increase of the Bachmann index, from 10.27 ± 2.29 at the basal visit to 16 ± 2.18 at final visit figure 4A. While the Sandvik index was significantly decreased, showing an improvement of incontinence symptoms at the end of the treatment, from 2.52 ± 2.61 to 1.09 ± 0.81, figure 4B. Also, pH measured showed a statistically significant decrease, from 6.68 ± 0.46 to 5.5 ± 0.56, which is closer to the healthy pH values (~4.5) in reproductive age women, figure 4C.

A statistically significant improvement of different domains of the FSFI was found, Arousal increased from 4.5 ± 4.13 to 7.06 ± 4.01, Lubrication from 6.64 ± 5.78 to 10.64 ± 6.16, Orgasm from 5.95 ± 3.75 to 8.23 ± 4.27, Satisfaction from 6.68 ± 4.30 to 8.83 ± 3.75 and Pain from 7.86 ± 5 to 4.32 ± 4.27 domains of the FSFI, Desire domain although experienced an increased punctuation, this was not statistically significant figure 5. The overall FSFI scale punctuation increased from 2.14 ± 1.45 to

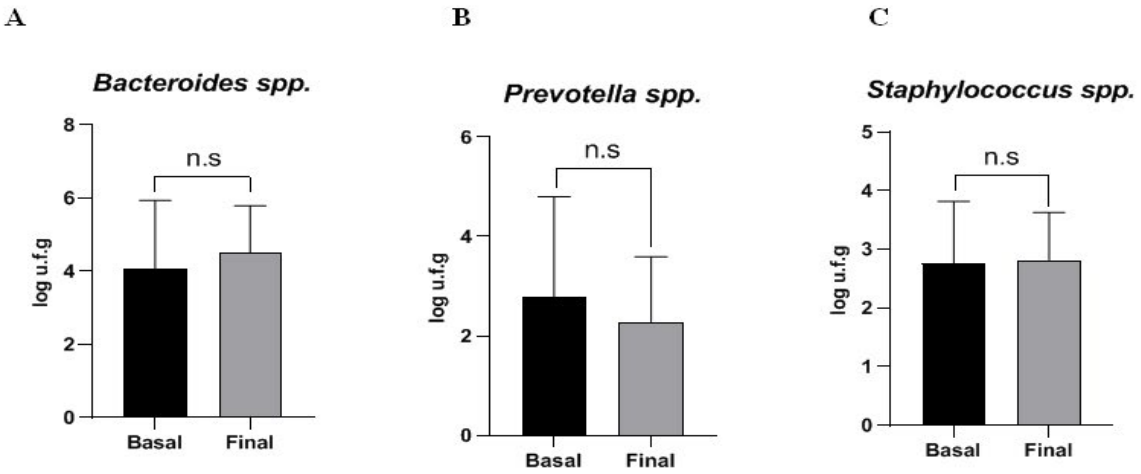

Figure 3: Non-lactic acid producing bacteria. Including Bacteroides spp., Prevotella spp., Staohylococcus spp. did not significantly changed after treatment, A, B and C respectively. n = 22; * p < 0.05, paired t-student with Welch's correction post hoc test.

Table 1: Average log u.f.g (± SD) at both basal and final visit and p values calculated, n = 22.

Organism	Basal visit	Final visit	p value
Lactobacillus spp.	4.01 (2.30)	4.61 (2.43)	0.0181
L crispatus	3.69 (2.21)	4.21 (2.29)	0.2987
L gaseri	1.83 (1.23)	2.51 (1.59)	0.0462
L jensenii	1.69 (1.39)	2.35 (1.20)	0.2680
L iners	2.49 (2.28)	3.91 (2.41)	0.0500
Lactic acid prod bacteria	4.74 (0.93)	5.31 (1.62)	0.1357
Bifidobacterium spp.	2.54 (1.36)	3.59 (1.63)	0.2666
Enterococcus spp.	4.98 (0.88)	5.09 (1.19)	0.3790
Molibuncus spp.	3.50 (0.93)	2.36 (0.54)	0.0826
Atopobium spp.	1.92 (0.95)	2.36 (1.61)	0.2556
Gardnerella vaginalis	3.68 (1.05)	3.93 (1.67)	0.1389
Non-lactic acid prod bacteria	5.57 (1.37)	4.66 (1.10)	0.3252
Bacteroides spp.	4.25 (0.99)	4.40 (1.25)	0.1932
Prevotella spp.	2.83 (1.34)	2.19 (2.19)	0.1252
Staphylococcus spp.	2.83 (1.34)	2.19 (1.15)	0.4154
Enterobacteriaceae spp.	3.23 (2.18)	2.54 (1.30)	0.0002

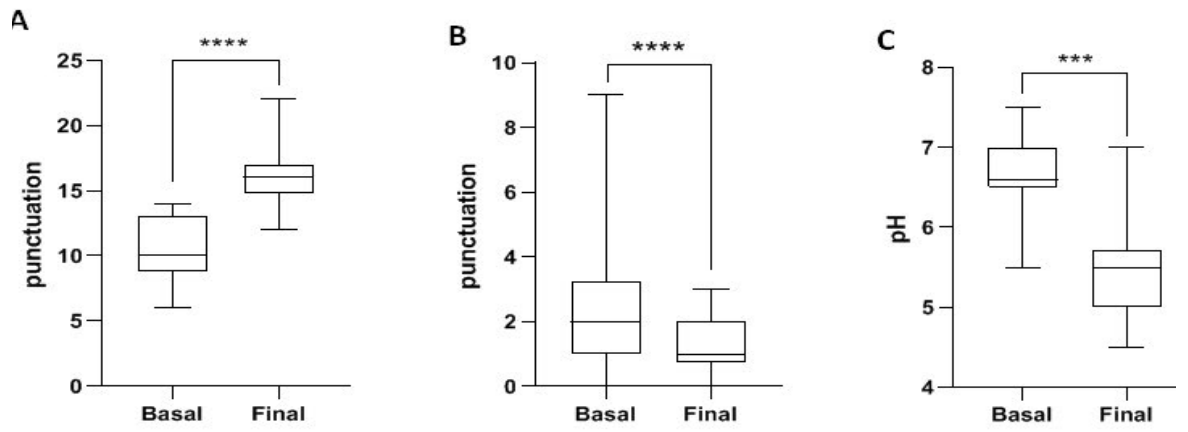

Figure 4: Changes in the Bachmann index: (A) Sandvik severity index; (B) and pH mean; (C) after treatment. *** $p < 0.001$, **** $p < 0.0001$, paired Mann-Whitney test for Bachmann and Sandvik indexes; *** $p < 0.001$ paired t-student with Welch's correction post hoc test for pH values. n = 22.

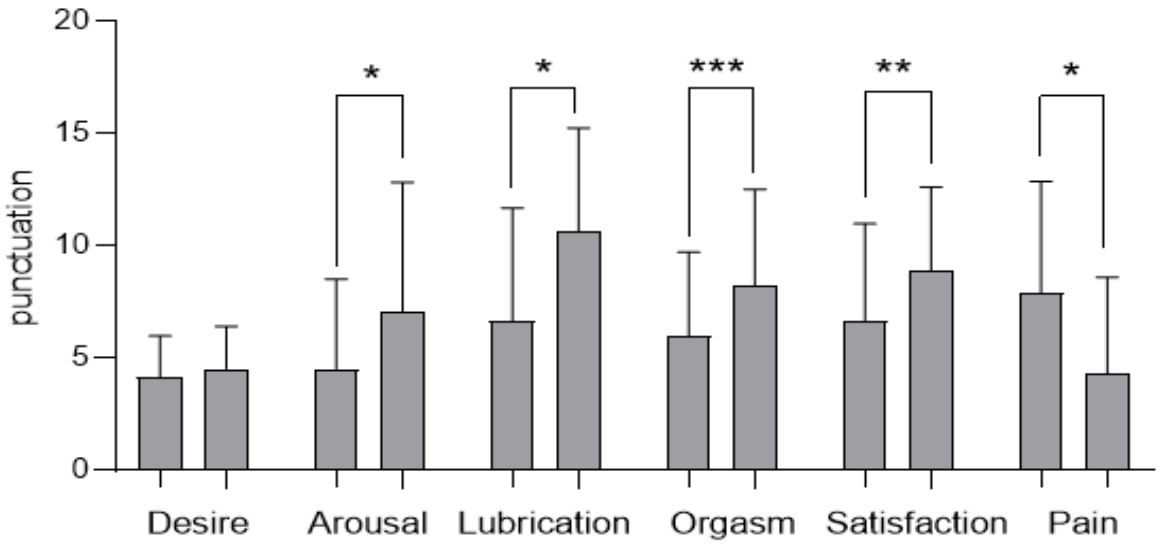

Figure 5: Changes in the Female Sexual Function Index after treatment. * $p < 0.05$, paired Mann-Whitney test for Lubrication; * $p < 0.05$, paired Student´s t-test with Welch's correction post hoc test for Arousal and Pain. n = 22.

3.08 ± 1.41, being statistically significant ($p = 0.0044$). Thus, 91% of women showed an improvement from basal visit to final visit punctuation in the FSFI.

Lastly, satisfaction level was assessed by means of a Likert scale, the average punctuation was 7.18 ± 1.15 and 95.5% of patients declaring that were satisfied or very satisfied with the treatment (Figure 6).

Discussion

It is expected than 17% of world population will be over the age of 65 by 2030. This implies that the social impact of GSM will keep increasing in the next years [1,2,23]. Hence, we wanted to report in this small series of clinical cases a novel approach for GSM management consisting in the combined treatment with fractional CO_2 laser and niosomal hyaluronic acid, *Centella asiatica*-based vaginal gel with hydrating, re-epithelizing properties. Our results are aligned with previously reported studies in which this therapeutic approach has a beneficial effect over the microbiota composition [12,24]. In this study Athanasiou, et al. [24] report that after 3 CO_2 laser sessions, there is a significant increase in the *Lactobacillus spp.* Nugent punctuation. This observation agrees with our results that, nonetheless, obtained a very similar result after 2 laser sessions (Figure 2A). This quicker result could be explained by the adjuvant effect of the niosomal hyaluronic acid, *Centella asiatica*-based vaginal which contains prebiotic (α-oligosaccharide, Bioecolia®), with already described positive effect reducing the Shannon index and increasing the *Lactobacillus spp.* content in the vaginal mucosa after 21 days treatment [25]. This effect could be particularly remarkable in combination with CO_2 laser, as it is known that certain topical treatments are potentiated due to the transitional increase of skin permeability after CO_2 laser treatment [20-22]. Interestingly, we found that *L. iners* was significantly increased (Figure 2C), this lactobacillus is

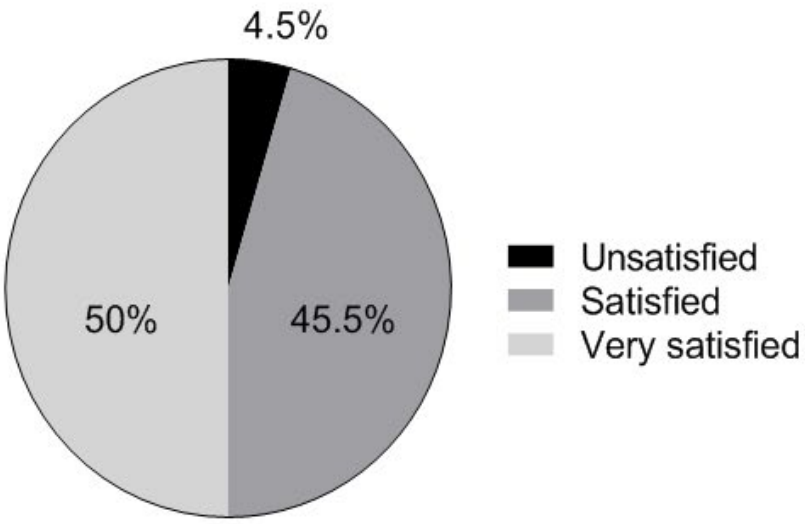

Figure 6: Percentage of patients reporting different satisfaction level with the treatment.

the predominant species in CST III which is associated with a transition towards a healthy microbiota (CST I, II and V). The other lactobacillus that we found a significantly increased is *L. gaseri* (Figure 2B), which is the preponderant species in CST II [26,27]. This increase in the lactobacilli, may explain the reduction of other bacteria measured in these patients such as *Enterobacteriaceae spp*. (Figure 2I). Controlled studies with bigger cohorts are needed to confirm these results that will add new data about the effect of CO_2 laser treatment on the microbiota which we know is an important aspect of GSM. However, some authors already reported that fractionated CO_2 laser improves vaginal microbiota to a pre-menopause composition in women with GSM [12,24].

Laser treatment also triggers collagen synthesis and remodelling, new vessel formation as well as increased glycogen load in the vaginal mucosa [16]. These changes favour the colonization of the mucosa by *Lactobacillus spp*., which are lactic acid producer bacteria. In reproductive women healthy vaginal pH is < 4.5, this is a consequence of the high lactic acid concentrations [26,28]. It is described that lactic acid specially the D isomer has got microbiocidal activity which protects women from different vaginal infection and prevents from vaginal dysbiosis [29]. Our results show a significant reduction of the vaginal pH from 6.68 ± 0.46 to 5.5 ± 0.56 (Figure 4C), which is closer to the vaginal pH in reproductive women (pH < 4.5). These results are aligned with our observation that after treatment *Lactobacillus spp*. concentration is increased, generating a healthier vaginal environment.

Other parameters related with vaginal health can be behind the improvement in the Bachmann vaginal health index (BVHI), which considers aspects such as vaginal elasticity, fluid volume, pH, epithelial integrity and moisture [30]. Our results agree with previously reported data showing that laser treatment can improve BVHI (Figure 4A). Importantly, the quicker response compared to other publications, could be a consequence of the summatory effect of the fractionated CO_2 laser with the *Centella asiatica* extract, which is known to potentiate the collagen synthesis and tissue remodelation after the inflammatory response [31,32]. These properties closely relate with the wound healing activity traditionally assigned to *Centella asiatica* and is expected to improve aspects such as elasticity and epithelial integrity [32,33]. BVHI also showed a significant improvement of vaginal dryness (Figure 4A), for which moisturizing agents are one of first line treatments. Hyaluronic acid (HA) is one of the most frequently used moisturizing agent for vaginal dryness, as it is an endogenous component of the extracellular matrix with hygroscopic capacity. There are a big number of clinical studies proving the efficacy of HA increasing the vaginal health, as well as using HA as an adjuvant treatment of CO_2 laser [34,8,35].

Interestingly, laser treatment increases skin permeability enhancing the penetration of compounds such as hyaluronic acid or *Centella asiatica* potentiating their properties [36]. Altogether, this combined treatment can justify not only the improvement of vaginal microbiota composition, but also BVHI, vaginal pH and Sandvik index. In this series of clinical cases, there found that a significant proportion of patients with urinary incontinence, measured with the Sandvick index which was improved at the end of the treatment from 2.52 ± 2.61 to 1.09 ± 0.81 (Figure 4B). Some studies have related mucosal improvement after laser with urethral coaptation [37-39], some other authors related the mucosa thickness and vascularization with an improvement of urinary incontinence [40]. These studies support not only the Sandvik punctuation improvement, but also indirectly the BVHI as factors that impact vulvo-vaginal health also affect urinary incontinence, such as compromised vaginal elasticity

[38-41]. Bibliography supports the notion that asiatic acid and asiaticoside present in the *Centella asiatica* are help the vascularization, and tissue remodelation processes, particularly if they are combined with the HA and the laser treatment [42].

The last parameter that was measured apart from the tolerability was the FSFI, which has already been reported to improve after CO_2 laser treatment [43,44]. Also, HA treatment due to its moisturizing activity has a beneficial effect over the dyspareunia [8]. However, it is important to note that those parameters that had a significant improvement (lubrication, pain, and arousal) can be seen as a direct consequence of better epithelial health, as this will increase the lubrication, resulting in a reduction of pain, both having an impact on arousal. It is now well accepted that alterations of sexual function undermine women's QoL, menopause is a risk factor to develop sexual function problems [45,46]. As women tend to spend a third of their lives on menopause, due to increased life expectancy it is important to advance in the management of menopausal symptoms that impact sexual function, further increasing women's QoL. This integral management will help us to move from the classical view of simply preventing the hot-flashes and osteoporosis to a more satisfactory management that takes into account also the will of a patient that want to keep her lifestyle and maintain her QoL during what now is a considerable period of her live [47].

Conclusion

To summarise, the observation we made in these patients agrees with previously published studies. The quicker effect we may observe not only re-equilibrating the microbiota composition but also improving other symptoms typically associated with the GSM such a reduction in the Bachmann and Sandvik indexes, pH equilibration and FSFI improvement might be due to a complementary effect between the CO_2 laser and the niosomal HA, *Centella asiatica* based vaginal gel. The combination of CO_2 laser and a niosomal HA, *Centella asiatica*-based vaginal gel may be a useful therapeutic tool for the management of GSM symptoms. We aim that this series of clinical cases add new data about the effectivity of CO_2 laser and supports the development of controlled clinical studies with bigger cohorts to confirm that niosomal hyaluronic acid, *Centella asiatica*-based vaginal gel might be excellent adjuvant tool together with laser treatment.

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